8 GLUCOSE METABOLISM, INSULIN, AND DIABETES

Learning objectives

- To have an understanding of the fate of glucose in organisms
- To understand the underlying causes of diabetes
- To be able to discuss the production and function of insulin
- To understand how the insulin receptor functions
- To be able to discuss the aspects of the signalling pathways downstream of insulin perception.

Introduction

Glucose is an immensely important molecule in cells. It is used in metabolism, is stored so that it can become available when needed, and is used for structural components in some organisms. In mammals, circulating glucose is tightly controlled, being regulated by hormones such as **insulin** and **glucagon**. Complex signalling and metabolic pathways regulate the storage and use of glucose, and when such pathways dysfunction a range of diseases can occur, but the most commonly known, and best studied, is **diabetes**.

Insulin is a hormone which is instrumental in the control of carbohydrate metabolism, and in particular the control of glucose levels. It is a peptide hormone produced by the **Islets of Langerhans** in the pancreas. It is released into the bloodstream and then sensed by cell surface receptors, in cells of the liver, muscle, and fat tissues, for example. One of the main responses by cells is the increased uptake of glucose, enabling it to be stored or used for energy-producing metabolism (ATP generation). Glucose is the first substrate of glycolysis, and hence a valuable source of carbohydrate, which can be oxidized, ultimately to carbon dioxide.

Unfortunately, as with all cell signalling, the processes may go wrong. Dysfunction of insulin signalling can lead to **diabetes**. There are two types, type 1 and type 2, the latter often being caused by life style, such as diet or lack of exercise. Both can be devastating conditions, which can lead to death. Many famous people have died from diabetes, or complications caused by it, while others have had amazing careers despite of it. They include Thomas Edison, one of America's greatest inventors, the inventor Alexander Graham Bell, the sports person Sir Steve Redgrave, and the UK prime minister Teresa May. Ella Fitzgerald, the famous jazz singer, suffered from diabetes, which caused her to have both her lower legs amputated, and she died eventually from a stroke. It can be a long-term and life-crippling disease.

8.1 The fate of glucose in organisms

Glucose is immensely important for cells (this is covered by the Primer by Bowater *et al*., see reading list below). The first step of **glycolysis** is the conversion of glucose to glucose 6-phosphate which initiates what may be considered mainstream metabolism, culminating in the production of pyruvate and acetyl coenzyme A (**acetyl-CoA**). Although some ATP is produced by glycolysis, the oxidation of acetyl-CoA through the **Krebs cycle**, and the products being used by **oxidative phosphorylation**, generates the majority of ATP for cellular activity. All this metabolism can start from glucose (of course, fatty acid metabolism and amino acid metabolism can feed into this pathway too).

Cells therefore need to have a ready source of glucose. This can be maintained from endogenous processes in plants, and from the diet in animals, and then by glucose storage. In plants, when conditions are good for **photosynthesis**, glucose can be stored as **starch**, with a good example being the storage of starch in potato tubers. They are a great source of carbohydrate for the human diet. As starch is broken down, the released glucose will help supply our metabolism. When conditions are unfavourable for endogenous glucose production in plants, those stores can be drawn from to maintain cellular activity. Plants also use glucose to make other sugars, such as sucrose (a covalent attachment of glucose and fructose), which is accumulated in fruits. Again, this is an excellent source of sugars for animal diets, including ours.

For animals, in times of plenty when there is a ready food supply, glucose can also be retained and stored. Then, and when food is not available again, the reserves can be used. Much excess carbon is stored in animals as fat (triglyceride) in the adipose tissues, and then can be released back to feed into metabolic pathways—acetyl-CoA is a vital branch point for such metabolism. However, glucose is also stored as **glycogen**, mainly in the liver and muscles. The control of glycogen metabolism was used as an example of a signalling pathway mediated by cAMP in Chapter 4 (look at Figure 4.3). In that scenario, adrenaline was perceived at the plasma membrane and the signal transduction pathway initiated led to the activation of **phosphorylase**, so increasing glycogen breakdown and increased glucose availability. At the same time, cAMP inhibited **glycogen synthase**, stopping free glucose from being re-polymerized into glycogen—hence, stopping a futile cycle. Free glucose created can then feed the metabolic processes needed in the cell, as discussed above. Dysfunction of glycogen metabolism can lead to a number of diseases, including von Gierke's disease, Pompe's disease, Her's disease, and McArdle's disease.

However, to allow glucose to be readily available for cells, a circulatory concentration of glucose is maintained via the blood. In fasting humans, the glucose concentration is approximately 4–7 mmol/L. If it is too low, the cells would not have enough glucose available to take in and metabolize; too high and glucose becomes toxic, leading to vascular disease and acute infections. Therefore, the release of glucose into the circulation, and its uptake from the circulation, has to be carefully controlled, and one of the main hormones involved in such regulation is insulin.

Key point

As well as being instrumental for metabolism, glucose can also be used to make structural molecules. In plants, glucose is used to make **cellulose**, which is a vital component of plant cell walls and helps to maintain the gross structures of plants as they grow.

8.2 An overview of diabetes

Diabetes is the common term for the condition **diabetes mellitus (DM)**. It is a disease which is caused by the abnormal functioning of insulin-mediated signalling. Minor symptoms include increased thirst and greater rate of urination. However, diabetes can lead to kidney disease and cardiovascular disease. Further damage can be seen to the nervous system, and the eyes, and cognitive functioning can be reduced. Skin problems may occur, such as ulcers, and in some cases limbs will need to be amputated as diabetes patients have a greater risk of gangrene. If diabetes is left untreated, death can result.

There are three main types of diabetes:

- **Type 1 diabetes mellitus (T1DM)**: this is the result of the Islets of Langerhans failing to produce enough insulin. It is an autoimmune disease, meaning that the immune system attacks itself. Destruction of the cells of the Islets reduces the ability of the pancreas to produce insulin and glucose levels can no longer be controlled properly.
- **Type 2 diabetes mellitus (T2DM)**: this type of diabetes is sometimes called non-insulin-dependent diabetes mellitus (NIDDM). If insulin is produced by the Islets but cannot be perceived and responded to by the recipient cells, then this will cause type 2 diabetes. This may be caused by a dysfunction of the receptor. There may be a problem with ligand binding, or a problem with the downstream signalling from the receptor.
- Gestational diabetes: this is sometimes seen in pregnant women who have high blood glucose levels.

There are many other, but rare, forms of diabetes and some can manifest later in life. For example, if the pancreas is damaged, insulin production can be reduced and diabetes-like symptoms develop.

Key point

Diabetes is not a single disease, but rather a group of diseases, focused around the dysfunction of insulin signalling.

8.3 The production and role of insulin

Insulin is a peptide hormone. It was named from the Latin for island, which is *insula*. When isolated, it can be seen to be two peptides held together by disulfide bonds. To see this at a molecular level, look at Figure 8.1. In panel C, there is a schematic of its structure, but, of course, in reality it will be a three-dimensional structure, as shown in panel D. This was a peptide structure studied by Dorothy Hodgkin at the University of Oxford for many years.

Although seen as two peptides, insulin is encoded for by a single gene. The initial translated product is known as preproinsulin (Figure 8.1A). The N-terminal of the peptide contains a signal peptide, and this directs the growing peptide and ribosome to the endoplasmic reticulum (ER). There, the polypeptide is pushed into the lumen of the ER, where the signal peptide is cleaved off by a peptidase which resides there, producing proinsulin (Figure 8.1B), now soluble in the ER. As the insulin is moved from the ER, through the Golgi apparatus to the storage vesicles, it is further processed. Three disulfide bonds

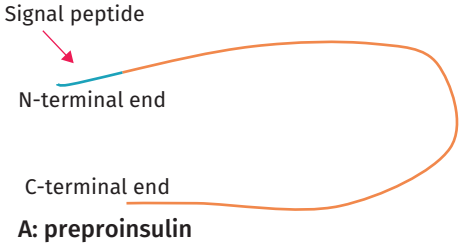
Scientific approach 8.1
X-ray diffraction

Scientists such as Dorothy Hodgkin solved the structure of proteins using a method called X-ray diffraction. This was used also by James Watson and Francis Crick to solve the structure of DNA (for which they were awarded the Nobel prize in 1962). Briefly, X-rays are fired at a crystallized form of the biomolecule of interest. This leaves a pattern on photographic film (digital today), which can be used to determine the distances between electron-dense structures in the molecule. It is not the only method which can be used to understand protein structures, but is still thought of by many as being the gold standard. Numerous proteins have now had their three-dimensional shape determined, and to visualize some of these it is worth visiting the RCSB database (www.rcsb.org).

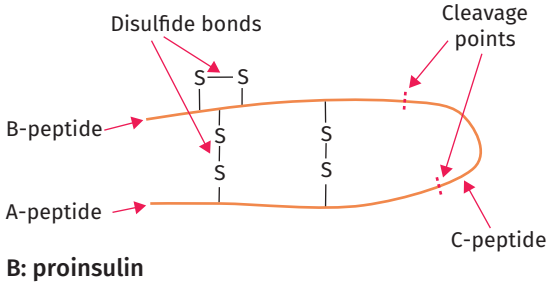
Discussion points:

- What are the other methods which can be deployed to solve protein structures? How do those methods compare to X-ray diffraction?
- Name three proteins for which the structures have been solved, and describe how this has increased our understanding of how the proteins function.

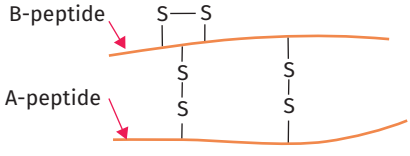
Fig. 8.1 Production and structure of insulin. Insulin is composed of two peptides, but is encoded for by a single gene. Therefore, post-translational modification needs to take place. A: the insulin gene encodes and is translated into a preproinsulin form. The signal peptide is removed to form proinsulin, as shown in B. This will form a structure stabilized by the formation of disulfide bonds. Proinsulin is cleaved, removing a large central section (C-peptide), to produce insulin, as shown in C. This has two peptides, held together by two of the disulfide bonds. D: the structure of human insulin as deposited in the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank at: www.rcsb.org/3d-view/3I3Z/1.



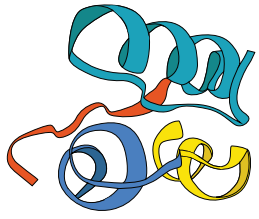
A: preproinsulin



B: proinsulin



C: insulin



D: insulin structure

are formed to stabilize its structure. Furthermore, two cleavage points enable a section to be removed. This is known as the C-peptide, and this leaves the B-peptide and A-peptide attached by two disulfide bonds (Figure 8.1C). This is the mature hormone, which is released.

However, insulin is not instantly released into the bloodstream, but rather, it is stored in vesicles in the cells. When needed, and triggered, the vesicles containing mature insulin are translocated to the plasma membrane. The cells in the pancreas sense an increase in extracellular glucose. Glucose enters the cells, leading to increased metabolism, and raised mitochondrial function. This leads to signalling, partly mediated by Ca^{2+} ion signalling (see Chapter 4) which initiates the vesicle movement, i.e. exocytosis. When it reaches the plasma membrane, the vesicle membrane fuses with, and becomes part of, the plasma membrane. The outcome of this is that the vesicle contents are secreted to outside the cells. The vesicle contents, by default, become part of the extracellular media. Once released, the hormone is transported by the circulation system to be perceived by other cells.

Alternatively, extracellular hormones may also have an effect on the release of insulin by the Islet cells. This is also probably mediated by Ca^{2+} ions, but other signalling components, such as G proteins, may also be involved. Insulin will be perceived on target cells by the presence of an **insulin receptor**, as in Figure 8.2. This can lead to the triggering of a signal transduction pathway, which initiates the movement of vesicles to the plasma membrane, in a similar manner to insulin's own release. Here, however, the important proteins are the glucose channels, called **GLUT4**, which are embedded in the vesicle membrane. When the vesicles fuse with the plasma membrane, the vesicle membrane, as before, becomes part of the plasma membrane, so leaving the GLUT4 proteins as part of that membrane. This increases the GLUT4 proteins on the cell surface, and as their function is to transport glucose, the capacity for the cells to take up glucose is significantly increased (Figure 8.3). This is the response that the release of insulin required.

Before leaving insulin, it is worth considering what happens to the C-peptide which is cleaved off proinsulin when mature insulin is made. It is generated in the same amounts as insulin and it is secreted. Evidence supports the role of

Fig. 8.2 The release and perception of insulin. Insulin is stored in vesicles in the pancreatic cells and released by exocytosis when required. The circulating insulin is perceived by cell surface receptors on the cell, which needs to respond. Dysfunction of either of these processes can cause diabetes, as shown.

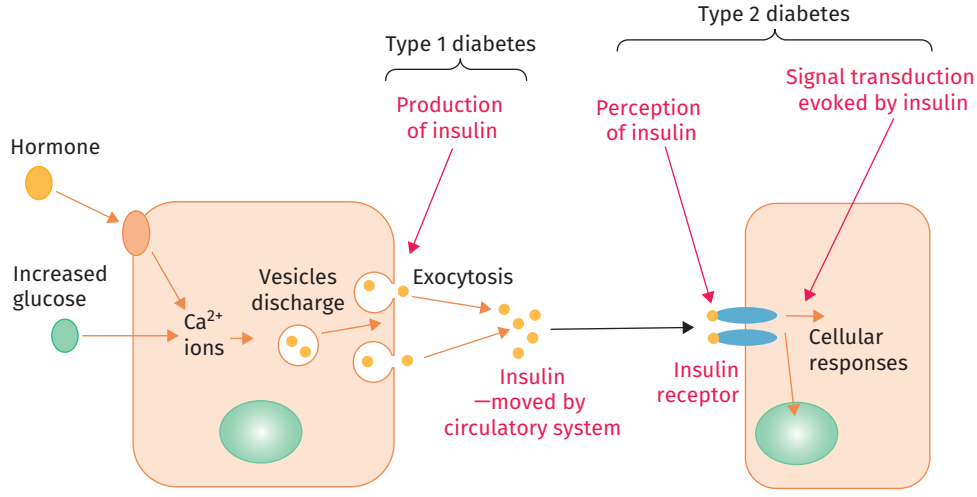
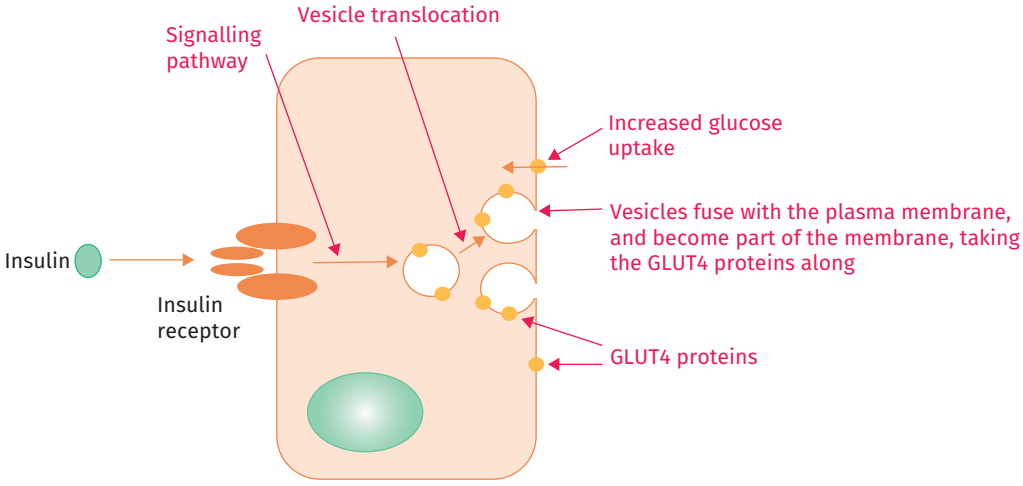


Fig. 8.3 Insulin can lead to increased glucose uptake. Insulin can initiate signalling which controls the translocation of vesicles to the plasma membrane that deliver GLUT4 proteins. GLUT4 are glucose transport proteins, so the more that there are in the plasma membrane, the more glucose the cell can take up.



C-peptide as a signal which is independent of insulin. It can be perceived by cells by the use of a G protein-coupled receptor (GPCR), downstream of which there may be Ca^{2+} ion signalling, and generation and influence of nitric oxide (NO). The use of C-peptide has been suggested as a therapy, especially for kidney disease.

Key point

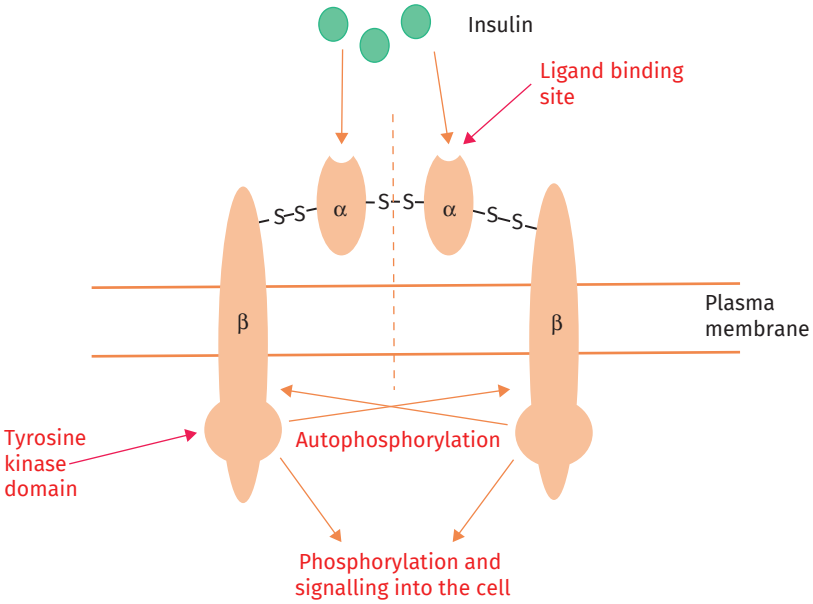
It is worth noting that insulin is actually part of a family of related proteins. Other family members include insulin-like growth factor-1 (IGF-1), which is produced in the liver, and a protein called relaxin, which is secreted by the placenta.

8.4 The insulin receptor

Insulin is perceived by cells using the insulin receptor. It resides at the plasma membrane and, like other receptors that are found there (see Chapter 2), it has three important regions: extracellular to bind the ligand, in this case insulin; transmembrane, which allows structural changes to transmit the message into the cell; and intracellular regions to propagate the message.

The insulin receptor is a receptor tyrosine kinase (RTK), as discussed in Chapter 4. In that discussion it was said that these RTKs dimerize on activation (look back also at Figure 3.1). However, this is not the case for the insulin receptor, as you can see in Figure 8.4. This shows that the insulin receptor is in fact a tetramer, i.e. made up of four subunits. However, look closely and you will see that it has two alpha subunits and two beta subunits, so has a $\alpha 2\beta 2$ structure. If we consider one α subunit along with one β subunit as a unit, then we can see that it does have a structure similar to a dimer, as two of these units are together. It can be considered as a dimer of dimers. However, there is no

Fig. 8.4 A schematic representation of the insulin receptor. The receptor has four subunits: two α and two β, held together by disulfide bonds. Ligand binding leads to phosphorylation events on the other side of the membrane.



dimerization event; that is, the subunits do not come together on activation. Rather, they are already held in this structure by disulfide bonds. The α subunits are responsible for insulin binding. This activates the receptor, and conformational changes transmitted through the β subunits activate the intracellular domains of the receptor.

As mentioned, the insulin receptor is a RTK. That means that the intracellular domains of the β subunits are tyrosine kinases. Also, as seen with other RTKs (see Figure 3.1) the intracellular domains are RTK substrates. This means that the receptor can autophosphorylate, perhaps ensuring that its signalling is prolonged. However, there are other substrates of the kinase domain. The most notable is one simply called **insulin receptor substrate-1 (IRS-1)**, whose function will be discussed below.

Turning off the insulin receptor will require that the ligand is released and that the phosphate groups are removed. The latter would be carried out by a tyrosine phosphatase (see Chapter 3). The receptor will also be internalized into the cell and translocated to early endosomes, using the mechanisms which were discussed in Chapter 2. There is then the opportunity for the receptors to be recycled and reused, allowing another round of insulin signalling.

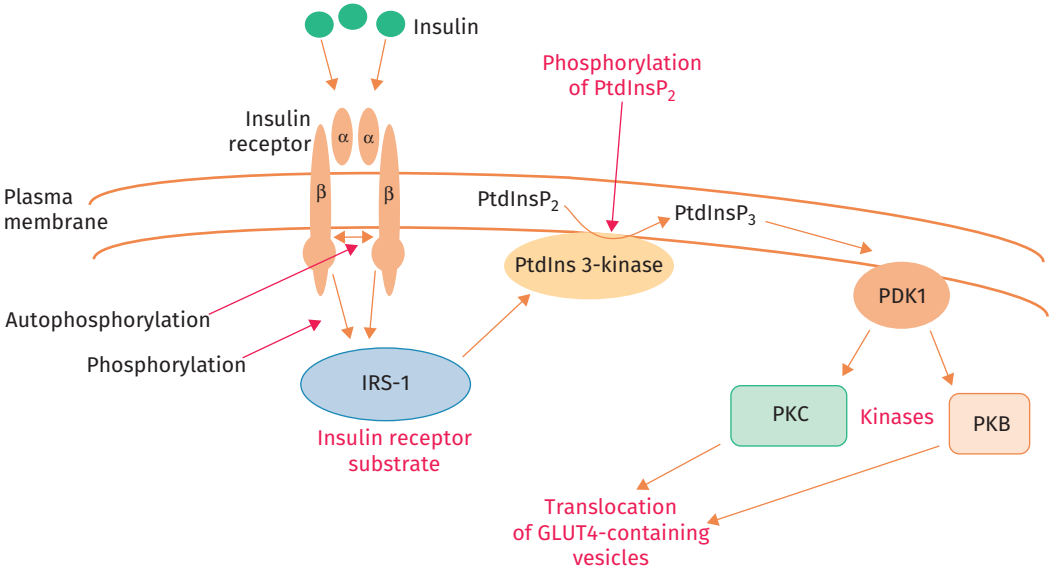
Key point

The insulin receptor is a good example of a receptor tyrosine kinase, but it does not conform to the expected mechanism of dimerization. This is because it is already in a 'dimeric'-type structure, having a tetrameric α2β2 form.

8.5 Pathways downstream of the insulin receptor

One of the cellular effects of the perception of insulin is the translocation of vesicles containing the glucose transporter, GLUT4, to the plasma membrane, which increases the capacity of the cell perceiving insulin to take up glucose. For this to happen, there has to be a signal transduction pathway initiated by the binding of insulin to its receptor. Figure 8.5 shows how the receptor binds to insulin and the receptor subsequently autophosphorylates. It also phosphorylates, on tyrosine residues, a separate protein called IRS-1. This can activate a protein called **PtdIns-3 kinase**. This is a kinase which has a substrate that is not a protein (note: this kinase would therefore not be referred to as a protein kinase). Here, the substrate is a membrane lipid, $PtdInsP_2$. Back in Chapter 4, $PtdInsP_2$ was a substrate for the enzyme PLC, and two signalling molecules were generated: $InsP_3$ and DAG. However, here, the $PtdInsP_2$ is not cleaved but has a phosphate group added, donated from ATP. The result is the formation of a new membrane lipid known as **phosphatidylinositol 3,4,5-trisphosphate ($PtdInsP_3$)**. This has an extra phosphate group added to position three of the inositol ring. The result is that $PtdInsP_2$ is converted to $PtdInsP_3$ and this change can be perceived by other components in the signal transduction pathway. $PtdInsP_3$ activates an enzyme called **3-phosphoinositide-dependent kinase (PDK)**, which is associated with the inner surface of the plasma membrane. On activation, this enzyme can activate further downstream kinases, including protein kinase C (PKC) and protein kinase B (PKB), which will phosphorylate proteins involved in the control of vesicle translocation. The result is the movement of the GLUT4-containing vesicles to the plasma membrane, which, of course, was the response needed on the perception of insulin on the outside of the cell.

Fig. 8.5 Insulin pathway which controls movement of GLUT4-containing vesicles. Activation of the insulin receptor leads to phosphorylation of IRS-1 and subsequent formation of $PtdInsP_3$. This activates a kinase cascade, which controls vesicle movement.



As discussed above, if elements of the signalling outlined in Figure 8.5 go wrong, diabetes can result. If the insulin is not made, so there is nothing for the receptor to perceive, the signalling pathway will not be initiated, and GLUT4 translocation will not take place. This would cause type 1 diabetes. If there is a problem with the insulin perception and receptor action, then type 2 diabetes would result. It may be that the ligand (in this case, insulin) simply cannot be recognized by the receptor, so the receptor is not activated. Alternatively, the ligand may bind but the receptor is not able to autophosphorylate, or not able to phosphorylate its downstream substrates. In this case, insulin would be perceived but there would be no subsequent downstream signalling. The result would be the same as if insulin had never arrived, as the signalling it tried to initiate failed.

There are several other downstream signalling components here, beyond the receptor, which may have a potential effect, and it is worth reviewing what would happen if these dysfunction. If PKC is taken as an example, it would be good to speculate whether a dysfunction of PKC in this pathway would lead to diabetes. A mutation could stop PKC either being activated or being able to carry out its catalytic role, i.e. phosphorylating downstream proteins. However, the role of PKC in all the signalling pathways in which it is potentially involved needs to be considered. Look back at Chapter 3, and it will be seen that the target sequence, or substrate, for PKC action is not uncommon. There are dozens of potential PKC target proteins, not only those used for GLUT4 translocation. Therefore, a dysfunctional PKC may have far more catastrophic effects than just stopping glucose uptake. It is possible that a PKC mutation would be so disastrous that the cells would not survive, and therefore the seriousness of the lack of normal functioning of this proteins is far worse than diabetes (not that that is trivial). Cells, and the organism, may not be able to live. This would be referred to as a **lethal mutation**, and so it may be unlikely that such proteins would contribute to the onset of diabetes. The same argument could be made, of course, for proteins such as PDK1 and PKB.

Insulin can also have effects in the nucleus of the cell, often if the insulin is at higher concentrations than would lead to other effects. Insulin can be considered to be a type of growth factor. Isoforms of insulin include insulin-like growth factor-1 (IGF-1), so such effects of insulin are not unexpected.

Look at Figure 8.6. There are large similarities to the pathways discussed before in other chapters, so look back at Figure 3.1 and compare this to Figure 8.6. As already discussed, as the insulin receptor is an RTK it can phosphorylate proteins downstream, including IRS-1. This can lead to the alteration of GRB2, which will activate the GEF Sos, which will activate the G protein Ras. Once Ras is activated, the kinase Raf will become active, leading to the activation of a MAPK cascade: MAPKK becomes active which phosphorylates a MAPK. Once the MAPK is active, it can translocate to the nucleus, where it will have its effects. Insulin has effects on gene expression and ultimately on cell growth, cell differentiation, and cell survival.

It can be seen, therefore, that insulin can have two quite different effects, and these are sometimes referred to as the **metabolic pathway** and the **mitogenic pathway**, as depicted in Figure 8.5 and Figure 8.6. However, like all cell signalling pathways, these representations have been simplified and there are other signalling components which can interfere and have a significant influence through **crosstalk**.

Fig. 8.6 Insulin signalling to the nucleus. Activation of the insulin receptor leads to the phosphorylation of IRS-1. The adaptor protein, GRB2, along with the exchange factor, Sos, leads to the activation of a monomeric G protein, Ras. This activates a MAP kinase cascade, which transfers the message to the nucleus.

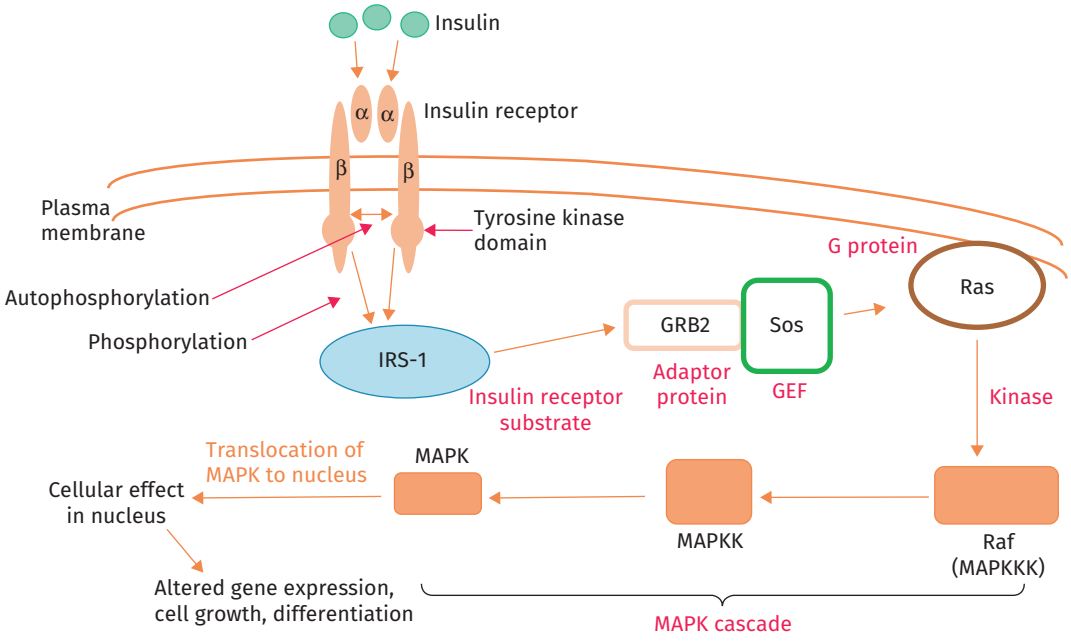
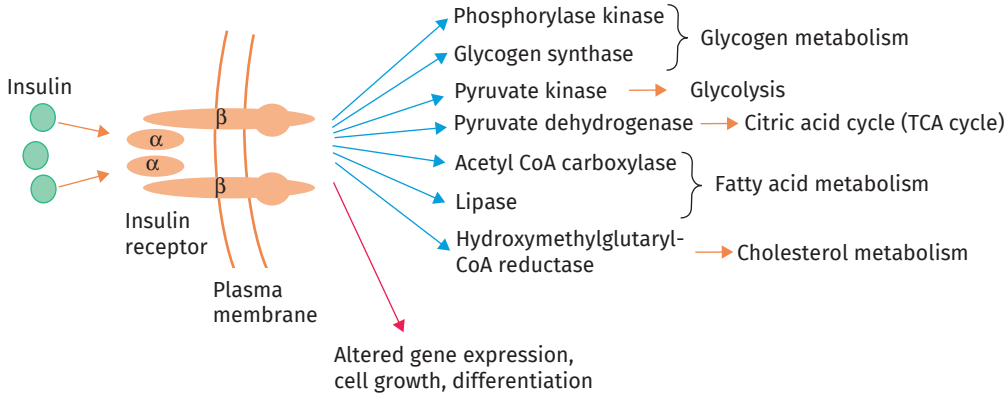


Fig. 8.7 Some of the intracellular effects elicited when a cell perceives the presence of insulin. Binding of insulin to the receptor can lead to a range of cellular responses, depending on the cell type. Metabolic pathway effects are shown with blue arrows, while the mitogenic pathway has a red arrow.



Diabetes, at a glance seems like quite a simple disease, caused by the dysfunction of a signal hormone pathway. However, insulin has multiple effects and extremely complex downstream signalling from its receptor, as you can see in Figure 8.7. Some of the metabolic enzymes which can be influenced by the perception of insulin are shown with the blue arrows. These include:

- glycogen metabolism, which dictates how much glucose is stored and how much is made available for metabolism and ATP production;
- metabolic pathways such as glycolysis and the citric acid cycle (CAC; TCA cycle; Krebs cycle). This will determine the flow of carbon compounds which are being oxidized by normal metabolism, which will influence the rate of ATP production, as well as other cofactors such as NADH;
- fatty acid metabolism, which will decide the volume of carbon compounds stored as triglyceride, or released for further oxidation and hence ATP production. A key factor in fat metabolism is the use of acetyl-CoA, and whether the two acetyl carbons are oxidized or stored.

On top of this is the mitogenic pathway. Therefore, it can be seen that insulin has a wide range of effects, and hence why its production, release, and perception is so important. This also highlights why diabetes is so hard to treat and manage as a disease.

8.6 Glucagon and its signalling

Glucagon is a peptide hormone comprising twenty-nine amino acids (look back at Table 2.1). It is produced in the α cells of the pancreas, and its effects are opposite to that seen with insulin: it raises circulatory glucose and fatty acids.

Glucagon is perceived on cells, for example at the liver, by a GPCR, as discussed in Chapter 4. This leads to the activation of a heterotrimeric G protein, the activation of adenylyl cyclase, and the increased intracellular concentration of cAMP. Many of the effects are mediated downstream by the kinase PKA, and hence glucose metabolism can be controlled. PKA can also phosphorylate a protein called **cAMP response element-binding protein (CREB)**. This protein is a transcription factor and will bind to DNA at specific regions known as **cAMP response elements (CRE)**, and so the levels of gene expression can be altered. CREB is also a target for other signals. It can be phosphorylated by kinases other than PKA and is involved in mediating signals initiated by noradrenaline and serotonin, for example.

Therefore, many of the effects of glucagon are influenced by the presence of other hormones too, such as insulin. Of course, exactly which cells can respond to the circulatory levels of such hormones will be dependent on the presence of the correct complement of receptors on the cell surface (as shown in Figure 2.2).

Key point

The levels of circulating glucose and related metabolic processes are not just under the control of glucagon, but rather glucagon is part of a complex web of signalling, which includes insulin, which ensures that the metabolic rates, and supply of substrates, is appropriate for the cells in an organism. When this goes wrong, conditions such as diabetes can result.

Chapter summary

- Glucose is a vital metabolite which needs to be available for cells to function properly.
- Glucose can be stored as starch (plants) or glycogen (animals), as well as being used to make structural components such as cellulose.
- Diabetes (diabetes mellitus) is a disease caused by a dysfunction of insulin signalling.
- There are three main forms of diabetes: type 1 (T1DM) caused by production dysfunction; type 2 (T2DM) caused by lack of perception of insulin; and gestational, seen in some pregnant women.
- Insulin is a peptide hormone, produced by the Islets of Langerhans in the pancreas. Although it is two peptides, insulin is encoded for by a single gene. The translated polypeptide (preproinsulin) is cleaved to produce proinsulin and then insulin. The remaining polypeptides are held together by disulfide bonds.
- The C-peptide of insulin also has signalling functions.
- Insulin can lead to the translocation of glucose transporters (GLUT4) in vesicles to the plasma membrane, so increasing a cell's capacity to take up glucose.
- Insulin is perceived by an insulin receptor, which is an integral plasma membrane protein. It is a tetramer, which can be considered as a dimer of dimers.
- The insulin receptor is an RTK, so will autophosphorylate and have other substrates for phosphorylation.
- Phosphorylation of IRS-1 can lead to the activation of PtdIns-3 kinase, which will phosphorylate the membrane lipid $PtdInsP_2$, leading to a cascade of kinases being activated. The result is translocation of GLUT4-containing vesicles to the plasma membrane and increased glucose uptake.
- Insulin has a wide range of effects in cells, including control of several metabolic pathways, as well as effects in the nucleus, such as altered gene expression.
- Glucagon has the opposite effects to insulin, as it increases circulatory glucose and fatty acids.
- Glucagon is perceived by a GPCR, with effects mediated by cAMP and PKA. It can also alter gene expression through control of CREB.
- Insulin signalling is influenced by crosstalk from other signalling pathways.

Further reading

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Discussion questions

8.1 Insulin is one member of a family of peptides. Find out and discuss what other insulin-like signalling molecules may do.

8.2 Compare and contrast the different types of diabetes. What would be a good rationale for the treatment of these different forms of the disease?

8.3 How conserved is the insulin sequence in mammals, and across a wider range of species?

8.4 Compare and contrast the signalling pathways initiated by epidermal growth factor and insulin.